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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/582,413	OHTOMO ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-59* is/are pending in the application.

4a) Of the above claim(s) *55-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-54 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/11/08,8/29/08,9/13/08,12/17/08,1/20/09,2/23/09.

DETAILED ACTION

1. The amendment filed April 8, 2009, is acknowledged and has been entered. Claim 55 has been amended.

2. The species election filed April 8, 2009, is acknowledged and has been entered.

Applicant has elected the species of invention wherein the antigen is myeloproliferative leukemia virus oncogene (mpl). In this response, Applicant has submitted that "Mpl is a member of the hematopoietic receptor family". Accordingly, hematopoietic receptor family antigens have been rejoined with the elected mpl species of antigen.

3. Claims 40-59 are pending. Claims 55-58 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 40-54 and 59 are under examination.

Priority

5. With regards to the issue of priority, at page 8 of the response filed June 30, 2008, Applicant indicates that a certified translation for the foreign priority document has been submitted.

While the certified translation for the foreign priority document is acknowledged, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In this case, as set forth below, new claims 40-54 and 59 have necessitated new rejections under 35 U.S.C. § 112, first paragraph. Accordingly, the effective filing date of claims 40-54 and remains the filing date of the instant application, namely October 26, 2006.

Information Disclosure Statement

6. The references cited in the information disclosure statements filed on 6/11/08, 8/29/08, 9/13/08, 12/17/08, 1/20/09 and 2/23/09, have been considered.

Grounds of Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed June 30, 2008, or December 30, 2008, have obviated or rendered moot the grounds of rejection set forth in the previous Office action mailed March 31, 2008.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The rejection of claims 40-54 and 59 under 35 U.S.C. 102(b) as being anticipated by Fukishima et al (US PG PUB 2004/058393, 2004, as cited in the office action mailed January 4, 2008, is maintained).

Starting at page 11 of the amendment filed June 30, 2008, Applicant has traversed this ground of rejection.

As newly presented the claims are herein drawn to methods comprising (a) identifying an antibody that binds to an antigen; (b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid

sequence; and (c) producing an sc(Fv)$_2$ comprising two or more copies of the light chain variable region sequence and two or more copies of the heavy chain variable region sequence, linked via linkers, wherein the sc(Fv)$_2$ binds to the antigen and exhibits an activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence. The claims are further drawn to the antigen being myeloproliferative leukemia virus oncogene (mpl) and the activity is a thrombopoietin (TPO)-like agonistic activity, the antibody being human or humanized, or wherein the sequence of the sc(Fv)2 comprises, in order: the heavy chain variable region sequence, a first linker sequence, the light chain variable region sequence, a second linker sequence, the heavy chain variable region sequence, a third linker sequence, and the light chain variable region sequence. Notably, since the phrase "greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence" is indefinite for the reasons detailed below, the claims are broadly, but reasonably interpreted to include any diabody and not one necessarily comprising the same light chain variable region and heavy chain variable region of the sc(Fv)$_2$.

In the response, Applicant appears to argue that Fukishima et al do not anticipate the claimed invention because Fukishima et al teach an sc(Fv)$_2$ with lower apoptosis-inducing activity than a corresponding diabody, while the instant claims require that the sc(Fv)$_2$ have "a greater level of activity than the corresponding diabody".

In response to applicant's argument that Fukishima et al teach an sc(Fv)$_2$ with lower apoptosis-inducing activity, it is noted that the instant claims are not drawn to an apoptosis-inducing activity and furthermore the claims are not necessarily drawn to a corresponding diabody. Therefore, this argument was not found persuasive.

Notably, as set forth in the abstract, Fukishima et al teach, "Modified antibodies

containing 2 or more H chain V domains and or more L chain V domains of a monoclonal antibody which can transduce a signal into cells by crosslinking a cell surface molecule, thereby serving as an agonist. Because of being usable as agonists for signal transduction, these modified antibodies are useful as, for example, preventives and/or remedies for various diseases such as cancer, inflammation, hormone disorders and blood diseases" and methods of making such "modified antibodies" with steps that are materially and manipulatively indistinguishable from the instantly claimed method (see e.g., pages 4-6). Fukishima et al also teach that these modified antibodies containing 2 or more H chain V domains and 2 or more L chain V domains of a monoclonal antibody can be single chain polypeptides termed "sc$(Fv)_2$" (see e.g., page 4, right column). Furthermore, Fukishima et al also teach antibodies of the invention that include antibodies that bind the myeloproliferative leukemia virus oncogene (mpl) antigen and antibodies that bind the myeloproliferative leukemia virus oncogene (mpl) antigen which have a thrombopoietin (TPO)-like agonistic activity and that the activity can be greater than the original antibody (see e.g., page 19 and 22 and claim 13). Finally, Fukishima et al the antibody being human or humanized, or wherein the sequence of the sc(Fv)2 comprises, in order: the heavy chain variable region sequence, a first linker sequence, the light chain variable region sequence, a second linker sequence, the heavy chain variable region sequence, a third linker sequence, and the light chain variable region sequence (see e.g., pages 2 and 3 and Figure 34).

Once again since the claims broadly, but reasonably include an sc(Fv)2 with a greater level of activity than the level at which any diabody, such as e.g., a diabody that binds a different antigen and does not have agonist activity, the methods of Fukishima et al inherently produce an sc(Fv)2 which meet the activity requirement set forth in the wherein clause. Furthermore, it is noted that the "activities" and the "level" of these "activities" compared to a diabody that any given sc$(Fv)_2$ polypeptide has after being made by the process of Fukishima et al would be an inherent property of the polypeptide. In this case, the Office lacks the resources and facilities to determine what activities the sc$(Fv)_2$ polypeptides made by the methods taught by Fukishima et al would have as compared to the original antibody and to a diabody, and since the

methods taught by Fukishima et al are materially and manipulatively indistinguishable from the claimed methods, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed methods are different from the methods taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Therefore, absent a showing of any difference, the claimed methods and the methods disclosed by the prior art are deemed the same and Fukishima et al anticipate the claimed invention.

Accordingly, for these reasons and after careful and full consideration of Applicant's response, the rejection of claims 40-54 and 59 under 35 U.S.C. 102(b) as being anticipated by Fukishima et al, is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 40-54 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 40-54 and 59 are indefinite because they recite “greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence” in claims 40 and 41 or “each of which consists of one copy of the humanized light chain variable region sequence linked via a linker to one copy of the humanized heavy chain variable region sequence” in claim 59. This recitation renders the claims indefinite because the claims do not identify the origination of “the light chain variable region sequence” and "the heavy chain variable

region sequence" in the diabody. Are these sequences the same sequences used to produce the multimer or single chain polypeptide or can they be sequences from another antibody? The claims cannot be construed unambiguously without knowing the answer to this question. Thus, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(b) Claims 44 and 46 are also indefinite because they recite "thrombopoietin-like agonist activity". This recitation renders the claims indefinite because it is unclear and cannot be ascertained whether the activity being referred to agonizes thrombopoietin, whether the activity agonizes a molecular pathway in a similar manner to thrombopoietin, or if the agonist activity is thrombopoietin-like in some other way? The claims cannot be construed unambiguously without knowing how the activity is "thrombopoietin-like". Thus, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 40-54 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

In this case, new claims 40 and 41 recite the limitation, "exhibits an activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence" and new claim 59 recites the limitation "exhibits an activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the humanized light chain variable region sequence linked via a linker to one copy of the humanized heavy chain variable region sequence".

Applicant has indicated that support for this amendment can be found throughout the specification for example at page 2, lines 24 to 28; page 4, lines 11 to 12; page 6, lines 30 to 33; page 7, lines 17 to 24, page 27, lines 1 to 17; and Figures 2 to 8 at page 1, line 37 to page 2, lines 2 and 13 to 18; page 4, lines 2 to 3 and 11 to 12; page 27, lines 1 to 17 and 20 to 22; and Figures 2 to 8 and page 5, lines 7 to 11; page 5, line 19 to page 6, lines 21 to 29; and page 8, lines 15 to 16.

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support for the language of the claims.

In this case, while the specification at page two, lines 13 to 18 sets forth a method for enhancing the activity of an antibody, which comprises making the antibody into a single-chain polypeptide comprising two or more light chain variable regions and two or more heavy chain variable regions linked via linkers and while the specification at page 27 compares agonist activities of species of sc(Fv)2's to corresponding diabodies, support for reciting that the claimed method produces a subgenus of multimers or single chain polypeptides which exhibit an activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at

which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence or which exhibit an activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the humanized light chain variable region sequence linked via a linker to one copy of the humanized heavy chain variable region sequence could not be found in the specification as filed. In this case, the specification does not appear to provide any general disclosure that the methods as claimed would produce a subgenus of multimers or single chain polypeptides which exhibit "activities" as instantly recited. Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972).

Therefore, given the apparent difference in the breadth of the claims and that of the pertinent disclosures it is submitted that this clearly illustrates that such amendments have in fact introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. §112, first paragraph.

Additionally, claim 40 recites the limitation "producing a covalently linked scFv multimer".

Notably, as set forth above, while the specification discloses making the antibody into a "single-chain polypeptide", support for the broader recitation of a "covalently linked scFv multimer", which could include e.g., cross-linked diabodies that were not disclosed in the specification, could not be found in the specification as filed.

Therefore, given the apparent difference in the breadth of the claims and that of the pertinent disclosures it is submitted that this clearly illustrates that such amendments have in fact introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. §112, first paragraph.

Otherwise these issues might be resolved if Applicant were to point to other

disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

14. Claims 40-54 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description

requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this case, the claims are broadly drawn to diverse methods comprising (a) identifying an antibody that binds to an antigen; (b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; and (c) producing an sc$(Fv)_2$ comprising two or more copies of the light chain variable region sequence and two or more copies of the heavy chain variable region sequence, linked via linkers, wherein the sc$(Fv)_2$ binds to the antigen and exhibits an "activity" at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence. As drawn to the elected invention, the claims are further drawn to the antigen being myeloproliferative leukemia virus oncogene (mpl) and the activity is a thrombopoietin (TPO)-like agonistic activity, the antibody being human or humanized, or wherein the sequence of the sc(Fv)2 comprises, in order: the heavy chain variable region sequence, a first linker sequence, the light chain variable region sequence, a second linker

sequence, the heavy chain variable region sequence, a third linker sequence, and the light chain variable region sequence.

Notably, as a first point, as explained above, since the language set forth in the NEW MATTER rejection does not appear to find support in the specification as filed, one of skill in the art would not recognize that Applicant was in possession of the claimed methods.

Secondly, as drawn to the generic invention, the claims broadly recite a genus of "antibody activities" which must now be exhibited at a level greater than the level at which a diabody exhibits the same activity. Notably, antibodies can have an diverse number of different and unpredictable activities depending on the epitope bound as well as the particular immunoglobulin subclass, i.e., IgM, IgG, IgE, etc of the antibody such as inhibiting cell proliferation, increasing cell proliferation, activating antibody dependent cellular cytotoxicity, mediating complement dependent cytotoxicity, etc. For example, it is recognized in the art that depending on the epitope bound by an antibody on the antigen the antibody binds that some antibodies can inhibit cell growth while some antibodies can actually accelerate growth (see e.g., Stancovski et al (PNAS, 88: 8691-8695, 1991 (page 8693, column 1)). Notably, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teach that the reason that antibodies which bind the same antigen can have opposite effects is because it is well known that different biological effects are associated with epitope specificity of the antibodies (see entire document, particularly page 4656, column 2). Accordingly, since it is established in the art that there is a high degree of unpredictability in determining the activities of antibodies that bind any given antigen, one of skill in the art would also recognize that whether any particular activity of an antibody was increased as compared to some diabody by producing an sc(Fv)2 from a parental antibody would also be highly unpredictable. Furthermore, with respect to antibody activities such as activating antibody dependent cellular cytotoxicity and mediating complement dependent cytotoxicity which are broadly encompassed by the phrase "an activity" that is greater in the single chain polypeptide as compared to a diabody, since these "activities" are mediated by the Fc region of the parental antibody and these single chain polypeptides and diabodies do not recite any Fc region, one of

skill in the art could not immediately envision or recognize that the claimed method would produce a single chain polypeptide with these activities at a greater level as compared to a diabody.

Therefore, while one of skill in the art could take any parental antibody and determine the heavy and light chain sequence of the antibody, which would allow one of skill in the art to make an sc(Fv)2 from a parental antibody, one of skill in the art could not immediately envision recognize or predict whether any particular activity of the sc(Fv)2 would be greater than the diabody. As an example of this unpredictability, as recognized by Applicant in the response filed June 30, 2008, Fukishima et al (supra) teach a species of full-length antibody (MABL-2), a corresponding scFv dimer (i.e., diabody), and a corresponding sc(Fv)2 in assays for apoptosis-inducing activity that is less active than the corresponding diabody "MABL2-scFv " in inducing apoptosis (see Figure 43). While the instant claims do not recite an apoptosis-inducing activity, since the generic invention includes any activity, such an activity is encompassed and it is submitted that one of skill in the art would not recognize that Applicant was in possession of the claimed methods, because one of skill in the art would not immediately envision recognize or predict when following the claimed method would result in producing an sc(Fv)2 which has a greater activity than a diabody. Notably, the specification acknowledges the unpredictability in recognizing and predicting the level of any particular activity in an sc(Fv)2 as compared to a diabody when it states at page 27, “In addition, since the sc(Fv)2 which is linked by a linker is more stable, there is a ***possibility*** that it can confer a higher activity as compared with a non-covalent diabody”[1]).

For these reasons, as a whole, it is submitted that the specification would amount to no more than a mere invitation to the skilled artisan to *identify methods* as encompassed by the claims wherein antibodies made by such methods have some measurable activity or agonist activity as recited in the claims at a greater level than a diabody has the activity, and it is duly noted that the written description provision of 35

[1] Emphasis added

U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for identifying it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Accordingly, because the skilled artisan could not immediately envision, recognize or distinguish when practicing the recited method to make an sc(Fv)2 would result in an sc(Fv)2 with a greater activity, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed methods at the time the application was filed.

15. Claim 40-54 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** methods comprising steps as encompassed by the claims that have been disclosed in the prior art, **does not reasonably provide enablement for using** the full scope of the claimed methods to produce sc(Fv)2 polypeptides which have a greater level of an activity, an agonist activity or a TPO-like agonist activity than a diabody exhibits the same activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term

> "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In this case, the claim is broadly drawn to diverse methods comprising (a) identifying an antibody that binds to an antigen; (b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; and (c) producing an $sc(Fv)_2$ comprising two or more copies of the light chain variable region sequence and two or more copies of the heavy chain variable region sequence, linked via linkers, wherein the $sc(Fv)_2$ binds to the antigen and exhibits an "activity" at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence. As drawn to the elected invention, the claims are further drawn to the antigen being

myeloproliferative leukemia virus oncogene (mpl) and the activity is a thrombopoietin (TPO)-like agonistic activity, the antibody being human or humanized, or wherein the sequence of the sc(Fv)2 comprises, in order: the heavy chain variable region sequence, a first linker sequence, the light chain variable region sequence, a second linker sequence, the heavy chain variable region sequence, a third linker sequence, and the light chain variable region sequence.

For the reasons set forth in the above rejection of the claims, as failing to satisfy the written description requirement, it has been submitted that the specification would amount to no more than an invitation to the skilled artisan to discover the identity of other processes encompassed by the claims.

Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

As set forth in the above written description rejection, Jiang et al and Fukishima et al (both supra) evidence that there is a high degree of unpredictability in predicting the activity of antibodies *a priori* and a high degree of unpredictability in determining whether producing an sc(Fv)2 from a parental antibody will resulting in polypeptide with an activity greater than a diabody. Accordingly, while one of skill in the art would be able to make sc(FV)2 polypeptides as recited by the active steps, they would be subject to undue and reasonable experimentation to use the recited method steps to increase the level of activity of an sc(Fv)2 to a greater level than the level of activity of a diabody. Notably, for example, Fukishima et al teach that some sc(Fv)2 polypeptides will have less of a particular activity than a diabody, so it is submitted that one of skill in the art

would clearly be subject to undue experimentation to use the claimed methods to produce sc(Fv)2 polypeptides with greater levels of activity than a diabody in this case, because the specification presents no specific, no general guidance as to how to use the claimed methods to ensure that the an sc(Fv)2 polypeptide has greater activity than a diabody.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571)272-9935. The examiner can normally be reached on 7-4:30 M-F with alternate Fridays off, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached at (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
June 22, 2009